Carcinoembryonic Antigen as a Predictive Factor for Recurrence After Stereotactic Body Radiotherapy in Stage I Lung Adenocarcinoma

Asai K¹, Shioyama Y², Nakamura K³, Sasaki T⁴, Ohga S⁵, Yoshitake T², Nonoshita T³, Shinohara M⁶, Matsumoto K⁶, Hirata H⁵, Honda H¹
¹Department of Clinical Radiology, ²Department of Heavy Particle Therapy and Radiation Oncology, ³School of Health Sciences, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; ⁴Department of Radiology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan; ⁵Kitakyushu municipal medical center, Kitakyushu, Japan

Purpose/Objectives

Stereotactic body radiation therapy (SBRT) is generally accepted as one of the best alternative treatments for medically inoperable patients with stage I non-small cell lung cancer (NSCLC) (10). To get better treatment outcome, identifying high risk groups of recurrence and modifying treatment strategy is needed. The purpose of this study is to clarify the usefulness of pretreatment measuring serum carcinoembryonic antigen (CEA), widely accepted tumor marker for adenocarcinoma, to predict prognosis among patients diagnosed stage I lung adenocarcinoma treated with SBRT.

Material/methods

Patient eligibility

- Ninety-nine consecutive patients with histologically - proven primary lung adenocarcinoma treated with hypofractionated SBRT at Kyusyu University, between April 2005 and February 2012, were retrospectively reviewed.
- The indication criteria of SBRT for primary lung:
  1. identification of clinical stage I
  2. medically inoperable or refusal of operation
  3. lesions not adjacent to the hilus or the heart
  4. no contraindication for radiotherapy of the lung, for example, interstitial pneumonia or collagen disease.
- The inclusion criteria for this study were as follows:
  1. the prescribed dose was 48 Gy in 4 fractions
  2. at least 6 months follow-up after SBRT
  3. serum CEA was measured within 2 months before starting of SBRT.
- The serum CEA concentration of blood samples (electrochemiluminescence immunoassay “ECLIA”, Cobas, Roche, Diagnostics, Mannheim, Germany; cut-off limit, 3.2 ng/ml) were determined by commercially available test kits.
- 53 patients met our criteria.

Treatment and follow up

- Immobilization: stereotactic body frame (Engineering System Co., Matsumoto, Japan), which uses a rigid frame, vacuum pillow and thermoplastic body shell (25).
- When the respiratory tumor motion was over 1 cm, the patients were simulated and treated using a visual feed-back guided voluntary breath hold system to minimize intra-fractional tumor motion (26). The other patients were under shallow breathing during simulation and treatment.
- Three-dimensional RT planning was conducted using an Eclipse system, ver. 6.5 (Varian Medical Systems, Palo Alto, CA).
- Target delineation: GTV=CTV, ITV=CTV + internal margin, PTV=ITV + 5 mm in all directions, leaf margin: 5
- Beam arrangement: seven to eight coplanar and non-coplanar photon beams accelerated to 4-10 MV.
- The follow-up interval was initially one or two months after the completion of SBRT during the first 6 months, and then every three months during the first two years, and every four to six months thereafter. At each visit, patients took physical examination, blood tests and imaging studies, including chest radiogram and chest CT.

Evaluation and Statistics

The correlations of pretreatment serum CEA concentration and age, T-stage, clinical stage, smoking history were analyzed using the Student’s t-test. Cumulative rate of over all, progression-free survival (OS, PFS) and local control rate (LCR) were calculated using Kaplan-Meier method. Each clinical parameter was divided into two groups and the PFS was compared between the two groups using the log-rank test and Cox proportional hazard model. The difference of OS, PFS were compared between the high CEA group (CEA＞4 ng/ml) and the low CEA group (CEA＜4 ng/ml). The difference of PFS as to pretreatment CEA value was also calculated for each clinical stage. Statistical significance was defined as a P value = 0.05. Analyses were performed using the JMP(R) software (SAS Institute Inc., Cary, NC).

Table 1. Patient and tumor characteristics

<table>
<thead>
<tr>
<th>Age (median)</th>
<th>56y.o. – 92y.o. (78)</th>
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</thead>
<tbody>
<tr>
<td>Sex</td>
<td>male 36, female 17</td>
</tr>
<tr>
<td>T-stage</td>
<td>T1a:12, T1b:25, T2a:16</td>
</tr>
<tr>
<td>Clinical stage</td>
<td>I: 37, II: 16</td>
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<tr>
<td>Tumor diameter (median)</td>
<td>0.9 cm – 4.5 cm (2.5)</td>
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<tr>
<td>Follow up period (median)</td>
<td>6 mo – 84 mo (30)</td>
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<tr>
<td>Pretreatment CEA value (median)</td>
<td>1.0 ng/ml – 213.4 ng/ml (3.5)</td>
</tr>
<tr>
<td>CEA＞4.3 vs. CEA≤4.3</td>
<td>18 vs. 35</td>
</tr>
<tr>
<td>Smoking history</td>
<td>yes/ex-smoker/no</td>
</tr>
<tr>
<td>Age (median)</td>
<td>10/22/21</td>
</tr>
</tbody>
</table>

Results

- Three-year overall survival (OS), progression free survival (PFS) and local control rate (LCR) were 89.3%, 65.6% and 84.0%, respectively, with a median follow-up of 30 months. (Fig 1) Patterns of failure were local failure in 5, regional failure in 4, and distant failure in 10 patients. (Table2)
- Pretreatment CEA value is significantly high among smoker patients. No other clinical factors are significantly correlated with pretreatment CEA value (Table3).

Discussion

- The recurrence rate after SBRT for Stage I NSCLC was reported as 18% in T1, 41% in T2, respectively. (11) To get better outcome in high risk cases, it must be considered to increase treatment intensity, for example, radiation dose escalation, addition of systemic chemotherapy or molecular targeted drug.
- Matsuo et al. pointed out tumor diameter and sex as the significant factors of failure in SBRT for NSCLC. (12) Tumor diameter is generally used for cancer staging. In this study, we investigated other prognostic factor in addition to tumor diameter to identify high risk group more precisely.
- Sakao et al. reported increased serum CEA is a predictive factor for poor outcome after surgery in stage I adenocarcinoma. (13)
- As for stage I NSCLC, there are also some reports shows high pre/postoperative CEA value as a predictive factor for poor outcome after surgery. (14)
- In this study, high pretreatment CEA value is significant risk factor among Stage I A and not I B. The reason of this difference may be the small number of cases, because tumor size have a much grater impact on prognosis in Stage I B.
- Adjuvant chemotherapy with uracil-tegafur (UFT) improves survival among patients completely resected pathological stage I B adenocarcinoma of the lung. (15) As to SBRT, there is an on-going clinical trial to evaluate the safety of adjuvant chemotherapy in Japan. There is still controversy about the indication of adjuvant therapy for stage I NSCLC, because uncertainty in selecting the high risk group. This study indicate pretreatment CEA value can be useful in selecting candidates for adjuvant therapy.

Conclusion

The pretreatment serum CEA level can be a prognostic factor in patients with stage I lung adenocarcinoma treated with SBRT.

References